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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional): 224738

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to "Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450" [37 CFR 1.8(a)]

on April 24, 2006

Signature: /John Gase/

Typed or printed name: John L. Gase

Application Number	Filed
10/706,265	November 12, 2003

First Named Inventor: HWANG

Art Unit	Examiner
1654	Jennifer I. Harle

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

- [ ] applicant/inventor.
- [ ] assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)
- [X] attorney or agent of record. Registration number 47,590
- [ ] attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34 _____

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April 24, 2006
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NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

- [ ] *Total of _____ forms are submitted.

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REMARKS/ARGUMENTS

The Pending Claims

Claims 1-11 and 36-39 are currently pending. Claims 1-11 are directed to a method of inhibiting metastasis of a tumor cell, and claims 36-39 are directed to a method of inhibiting growth of a tumor cell.

Status of Pending Claims

Claims 1-11 and 36-39 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Koshiba et al., *Clinical Cancer Research, 6*, 3530-35 (2000) ("Koshiba") in combination with WO 99/50461 (Murphy et al.) ("Murphy") and WO 99/47158 (Clark-Lewis et al.) ("Clark-Lewis").

Discussion of the Section 103 Rejection

Koshiba discloses *in vitro* studies of T22, a CXCR4 antagonist, in cell migration assays. However, the disclosure of Koshiba does not provide one of ordinary skill in the art to use a CXCR4 antagonist, such as T22, to inhibit metastasis in a mammal *with a reasonable expectation of success*. In acknowledgment of this deficiency in the disclosure of Koshiba, the Office has withdrawn its earlier rejection of the claims over Koshiba alone (see Advisory Action dated February 23, 2006, continuation sheet, withdrawing Section 103 rejection over Koshiba alone in view of Applicants' Response to Office Action dated January 17, 2006).

Nevertheless, the Office maintains the rejection of the claims over Koshiba in combination with the Murphy and Clark-Lewis references, alleging that Murphy and Clark-Lewis provide the motivation with a reasonable expectation of success that is missing from Koshiba. The Office's analysis of how Murphy and Clark-Lewis provide such motivation with a reasonable expectation of success is set forth in the Final Office Action dated November 14, 2005, as follows:

> Both Murphy and Clark-Lewis disclose use o[f] CXCR-4 antagonist, of which T-22 is one, in animal models to inhibit metastasis of tumor cells and inhibit the growth of tumor cells. Moreover, since both Murphy and Clark-Lewis disclose CXCR-4 antagonists that have *in vivo* efficacy, [] there is a reasonable expectation of success that T22, which has the same mode of action in vitro, would react similarly *in vivo*.

(Final Office Action dated November 14, 2005 at pp. 4-5). The Office has provided no further analysis or reasoning on this point.

It is the Office's burden to come forward with evidence sufficient to establish a *prima facie* case in support of a Section 103 rejection. The Office has failed to meet its burden for several reasons. First, the Office has failed to consider the factors required to properly assess obviousness as set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966) ("the *Graham* Factors"). Second, the Office's stated reasoning as to why the Murphy and Clark-Lewis references provide motivation with a reasonable expectation of success is based on error in fact. Third, when the cited references are properly considered, they do not lead one of ordinary skill in the art to the claimed subject matter with a reasonable expectation of success. Each of these reasons is discussed in greater detail below.

A. The Office Has Failed to Consider the Graham Factors

Under section 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. *Graham,* 383 U.S. at 17-18, 148 USPQ at 467.

The Office has failed to appropriately ascertain the scope and content of the Murphy or Clark-Lewis references upon which it relies, or to consider the differences between the disclosures of these references and the subject matter of the claims. For instance, the Office alleges that both Murphy and Clark-Lewis disclose the use of "CXCR4 antagonists" to inhibit tumor growth and metastasis, but fails to cite to any portion of either reference to support its argument, or identify even a single species of the "CXCR4 antagonists" that are allegedly disclosed. The claims, save claim 11, are not directed to the use of "CXCR4 antagonists" generally, but rather to a CXCR4 antagonist having a particular chemical structure. Thus, the mere observation that Murphy and Clark-Lewis pertain generally to "CXCR4 antagonists" completely ignores significant elements of the claims, and fails to consider the differences that exist between the claimed invention and the prior art.

In fact, the disclosures of Murphy and Clark-Lewis are quite different from the subject matter of the claims. As discussed in greater detail below, Murphy fails to disclose the use of any particular CXCR4 antagonist, and the antagonists disclosed in Clark-Lewis bear no structural similarity to the compounds of the pending claims. Without ascertaining

the structure of the compounds disclosed in the cited references and considering the differences between those compounds and the compounds recited in the pending claims, it is impossible to fairly and appropriately determine whether Murphy or Clark-Lewis can be combined with Koshiba in such a way as to lead one of ordinary skill in the art to the claimed invention with a reasonable expectation of success.

The Office also has failed to consider, or even mention, the level of ordinary skill in the art as it existed at the time the present application was filed. The Office must ascertain what would have been obvious to one of ordinary skill in the art at the time the invention was made, and not to the inventor, a judge, a layman, those skilled in remote arts, or to geniuses in the art at hand. *Environmental Designs, Ltd. v. Union Oil Co.*, 713 F.2d 693, 697, 218 USPQ 865, 869 (Fed. Cir. 1983), *cert. denied*, 464 U.S. 1043 (1984). A determination of the level of ordinary skill is necessary to maintain objectivity and avoid the improper hindsight reconstruction of the claimed invention. *Al-Site Corp. v. VSI International, Inc.*, 174 F.3d 1308, 1324, 50 USPQ2d 1161, 1171 (Fed. Cir. 1999).

Thus, the Office has failed to properly consider any of the factors required by *Graham*. For this reason alone, the Office has not established *prima facie* obviousness under Section 103, and the rejection of the pending claims should be withdrawn.

B. The Office's Reasoning is Based on Error In Fact

The Office's stated reasoning in support of the Section 103 rejection rests in large part on the assertion that the Murphy and Clark-Lewis references disclose the use of CXCR4 antagonists to inhibit metastasis, and provide evidence of the effectiveness of such compounds *in vivo*. The Office cites no passage in either reference supporting its assertion, and, upon review of the references, Applicants' find no such disclosure.

Murphy only generally discloses the use of "CXCR4 antagonists" to treat various malignancies, including tumors. Murphy does not disclose any specific CXCR4 antagonist, much less the *in vivo* testing of CXCR4 antagonists. The only testing disclosed in Murphy is of anti-sense nucleic acids, which are not CXCR4 antagonists (see, e.g., Specification at para. [0018]), and are tested *in vitro* for interference with CXCR4 production. Murphy also fails to disclose the use of any CXCR4 antagonist to inhibit metastasis.

Clark-Lewis discloses *in vivo* testing of particular CXCR4 antagonists for inhibition of tumor growth, and states in the description of figures that lung sections were examined for metastasis (Clark-Lewis at p. 8, description of Figure 6). However, nowhere does Clark-

Lewis report the results of the examination for metastasis. Rather, Clark-Lewis reports only the effect of the antagonists on the volume of the primary tumor. Thus, contrary to the Office's assertion, it is unknown from Clark-Lewis whether CXCR4 antagonists can be used to inhibit metastasis.

Accordingly, the Office's reasoning is based on erroneous facts, and fails to establish *prima facie* obviousness under Section 103 for this additional reason.

C. When Properly Considered, Neither Murphy Nor Clark-Lewis Provide the Missing Teachings of Koshiba

When the cited references are properly examined, and the differences between the cited references and claimed subject matter properly considered, it is clear that neither Murphy nor Clark-Lewis can be combined with Koshiba in such a way as to lead one of ordinary skill in the art to the claimed invention with a reasonable expectation of success.

As previously mentioned, Murphy does not disclose any particular CXCR4 antagonist, much less the *in vivo* testing of such an antagonist. Murphy also fails to disclose the use of a CXCR4 antagonist to inhibit metastasis. Thus, Murphy adds nothing to the disclosure of Koshiba, and the combination of Murphy and Koshiba fails to disclose the claimed invention for the same reasons that Koshiba alone fails to disclose the claimed invention, which reasons are already of record.

Clark-Lewis discloses CXCR4 antagonists that are fragments of SDF-1, the natural polypeptide ligand of the CXCR4 receptor. However, the compounds of the pending claims, including T22, have no significant sequence identity to the antagonists disclosed in Clark-Lewis; they are entirely different polypeptides. Given these significant differences, one of ordinary skill in the art would *not* be led to reasonably expect the compounds to be interchangeable *in vivo*.

Furthermore, as mentioned above, Clark-Lewis fails to provide evidence that any CXCR4 antagonist could successfully be used to inhibit metastasis. Metastasis is a complex event distinct from tumor growth (e.g., Specification at para. [0004]); the Office does not dispute this premise. Although Clark-Lewis states in the description of the drawings that metastasis was examined in connection with *in vivo* testing, nowhere does Clark-Lewis report the results of the examination. Thus, contrary to the Office's contention, Clark-Lewis does not provide any evidence of the *in vivo* efficacy of a CXCR4 antagonist in vivo.

For the foregoing reasons, Clark-Lewis fails to provide the requisite motivation with a reasonable expectation of success missing from Koshiba, whether considered with Koshiba alone or in combination with Murphy.

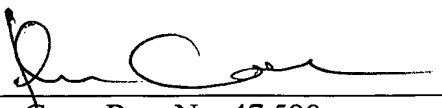
It is the Office's burden to substantiate its conclusion that the cited references can be combined with Koshiba in such a way as to render obvious the claimed invention; it is not the Applicants' burden to rebut the unsupported conclusion. *In re Rijckaert*, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). The Office ignores the substantial differences between the disclosures of Murphy of Clark-Lewis and that of Koshiba, and has thus failed to provide a sufficient rationale, much less any evidence, to support its finding of obviousness. Indeed, without impermissibly consulting the Applicants' own disclosure, one of ordinary skill in the art would not be led by the disclosures of Murphy or Clark-Lewis to use T22 or any other claimed compound to inhibit metastasis or tumor growth with a reasonable expectation of success. At best, these references might suggest to one of ordinary skill in the art to experiment with T22 or similar compounds, but an "obvious to try" rationale is insufficient to establish obviousness under Section 103.

For the foregoing additional reasons, the Section 103 rejection is improper and should be withdrawn.

Conclusion

Applicants' respectfully request withdrawal of the Section 103 rejection for the foregoing reasons.

Respectfully submitted,



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